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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,881	07/17/2006	Simone Charlotte Vonwiller	ALAR8.001APC	9163

20995 7590 06/24/2010

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EXAMINER	
PALENIK, JEFFREY T	

ART UNIT	PAPER NUMBER
1615	

NOTIFICATION DATE	DELIVERY MODE
06/24/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/552,881	VONWILLER ET AL.	
	Examiner	Art Unit	
	Jeffrey T. Palenik	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-70* is/are pending in the application.

4a) Of the above claim(s) *51-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-50 and 67-70* is/are rejected.

7)☒ Claim(s) *47 and 70* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application.
6) ☐ Other: _____.

DETAILED ACTION

STATUS OF THE APPLICATION

Applicants' amendments and remarks, filed 7 April 2010 regarding Application N° 10/552,881, are acknowledged and entered on the record. The Examiner acknowledges the following:

No claims have been cancelled.

Claim 70 has been added. Support is derived from the originally filed claims (e.g. claim 36).

Claims 36, 40, 41 and 44 have been amended. Claim 36 now recites that the polysaccharide is mixed with an alkaline medium with a "cross-linking agent consisting essentially of" a bifunctional "epoxide" or a polyfunctional epoxide. Claims 40, 41 and 44 simply replace the term epoxide with "cross-linking agent".

No new matter has been added.

Thus, claims 36-50 and 67-69 now represent all claims currently under consideration.

INFORMATION DISCLOSURE STATEMENT

No new Information Disclosure Statements (IDS) have been submitted for consideration.

WITHDRAWN OBJECTIONS/REJECTIONS

Rejection under 35 USC 112

Applicants' amendment to claim 36, removing the phrase "having a single type of cross-linkage", renders moot the new matter rejection, under 35 USC 112, first paragraph. Thus, said rejection has been **withdrawn**.

CLAIM OBJECTIONS

New claim 70 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. The limitation of the claim recites the process of claim 36 wherein the polysaccharide is contacted with one cross-linking agent. Turning to claim 36, step (a) already recites that the "polysaccharide [is] mixed in an alkaline medium with ***a*** cross-linking agent consisting essentially of ***a*** bifunctional epoxide or ***a*** polyfunctional epoxide". As the base claim already recites that a single cross-linking agent is used and that it is selected from one of two genera not specified in the dependent claim, the Examiner considers the newly added claim to not further limit claim 36.

Claim 47 is objected to because of the following informalities: it recites dependency from claim 67. The Examiner considers this to be a simple typographical error and for the purposes of examination herein, considers the claim as depending from claim 37.

Appropriate correction is required.

MAINTAINED REJECTIONS

The following rejections are maintained from the previous Office Correspondence dated 11 December 2009 since the art which was previously cited continues to read on the amended/newly cited limitations.

CLAIM REJECTIONS - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 36-41, 46 and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhao (WO 00/46253).

The instant claims are directed to a process for producing a cross-linked gel comprising mixing (e.g. contacting) an alkaline-based polysaccharide medium with an epoxide cross-linking agent via ether bonds, drying said gel without removing the ether bonds, washing the gel with a water miscible solvent and neutralizing said gel using an acidic medium (claim 1). The polysaccharide is further recited as hyaluronic acid or (HA) (claims 37-39). The epoxide is further recited as butanediol diglycidyl ether (claims 40 and 41). The mixing, drying and washing steps are recited as being performed under alkaline conditions with acetone (claims 46 and 47).

Zhao teaches a method for producing a cross-linked gel wherein an alkaline solution of hyaluronic acid in sodium hydroxide is mixed with varied volumes of the multifunctional

epoxide 1,2,7,8,-diepoxyoctane, drying said mixture into a gel formation, purifying (e.g. washing) the dried gel using acetone/water, acetone and isopropyl alcohol (IPA), and neutralizing said gel in an acidic medium of acetone/hydrochloric acid at pH 5 (Example 6 and claim 1). Claim 4 teaches additional cross-linking agents such as butanediol diglycidyl ether.

CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 36-50 and 67-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhao (WO 00/46253) in view of Mälson (WO 87/07898).

The instant claims are directed to a process for producing a cross-linked hyaluronic gel, as discussed above. Various conditions under which the procedure is performed such as pH (claim 42), component concentration (claim 43), and reaction and drying temperatures (claims 44 and 45) are recited. Claims 48 and 49 recite step (d.) as further comprising freeze-drying or

lyophilizing the produced gel and reconstituting it in phosphate buffered saline (PBS). The term "reconstituting", viewed in its broadest and most reasonable terms, is interpreted by the Examiner as reciting "restoration to a former condition by adding water". In the case of claim 49, this is interpreted as restoration using a water-based medium such as PBS. Claim 50 recites the gel as further comprising a biologically active substance.

The teachings to Zhao are discussed above. Zhao further teaches that the starting solution for an alkaline solution is preferably at a pH of 10 or more and that the reaction may effected at a temperature in the range of 15 to 50°C (pg. 9, line 27 to pg. 10, line 4). Example 6 further teaches that the starting solution is a 2.5% solution of hyaluronic acid in sodium hydroxide (HA/NaOH) which is mixed with varying amounts of epoxide. Tables 1-3 teach varying "feeding ratios" of HA to the cross-linking compound. Drying of the gel at a temperature of at least about 35°C (i.e. in a 37°C oven) is taught (Examples 1-3). Restoration of the gel product from a dried film or sheet format by immersing it in PBS is taught (pg. 11, lines 11-15). Incorporation of a biologically active substance into the gel is taught (claims 1, 15, 22 and 23).

Freeze drying as a means for drying the gel to a film or sheet format is not expressly taught by Zhao. Nor is it expressly taught that the gel is dried under a vacuum.

Mälson teaches the preparation of a cross-linked polymerized gel product (e.g. an insoluble, porous spongy material) wherein sodium hyaluronate or hyaluronic acid is dissolved into sodium hydroxide, mixed with 0.15 wt./volume % butanediol diglycidyl ether (BDDE),

washed (e.g. dialysed) with water and then dried to form the film under acidic conditions (Example 1 and claims 1-7). Example 9 expressly teaches drying the formulation using freeze-drying. Example 19 teaches incorporation of Vitamin A as a biologically active substance which is controllably released from said gel by immersion into a volume of buffer. "Physiological saline" such as PBS is taught as being used to swell or restore the gels (pg. 9, second paragraph; pg. 8, bottom paragraph).

Mälson does not expressly teach the steps of the method in order or all of the specific reaction conditions as instantly claimed (e.g. vacuum drying).

In view of the combined teachings of the prior art, one of ordinary skill in the art, at the time of the invention, would have been motivated to use the instantly claimed method in order to prepare a hyaluronic acid and epoxide cross-linked polymerized gel. Such would have been obvious in the absence of evidence to the contrary since Zhao expressly teaches the procedure with the exception of certain particular claimed parameters (i.e. compositional epoxide percentage, vacuum drying, or freeze-drying). With the exception of certain adjustable parameters, the art taught by Mälson overlaps in its teaching of method steps (e.g. alkaline starting solutions mixed with epoxides) and components (e.g. hyaluronic acid and butanediol diglycidyl ether) with Zhao, both of which can be incorporated to arrive at the instant method claims. Lyophilization, while not taught by Zhao, is a method which is well known in the art by the skilled artisan as a means for preserving gels as dehydrated films. Furthermore, though neither of the practiced inventions expressly teaches using a drying the gel preparations at higher temperatures using a vacuum drying oven, one of ordinary skill in the art would be well motivated to employ such an oven if for no other reason than to minimize the risk of particulate

contamination in the dried gel product.

Therefore, a person of ordinary skill in the art would have a reasonable expectation of success in modifying the gel-producing method practiced by Zhao with the freeze-drying gel preparation step taught by Mälson since the combined teachings disclose the instantly claimed method for producing a biologically active cross-linked gel composition. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

While neither Zhao nor Mälson teach the instantly claimed pH, temperature and percentage ranges, as instantly claimed by Applicants, Zhao offers a broader teaching of said parameters in the practiced Examples and Tables, as discussed above. Since the values and formats of each parameter with respect to the claimed composition are adjustable, it follows that each is a result-effective parameter that a person having ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. As evidenced by the combination of the two teachings, it would have been customary for an artisan of ordinary skill, for example, to adjust the amount of multifunctional epoxide-based cross-linking agent, in order to achieve the desired gel composition. Thus, absent some demonstration of unexpected results from the claimed parameters, optimization of any of these parameters would have been obvious at the time of Applicants' invention.

RESPONSE TO ARGUMENTS

Applicants' arguments with regard to the rejection of claims 36-41, 46 and 47 under 35 USC 102(b) as being anticipated by Zhao et al., as well as the rejection of claims 36-50 and 67-69 under 35 USC 103(a) as being unpatentable over the combined teachings of Zhao et al. and Mälson et al., have both been fully considered, but neither are persuasive.

Applicants' allege that Zhao teaches away from the instant invention on the grounds that a molecule of hyaluronic acid (HA) is cross-linked to another molecule of HA by means of **two different types of functional bonds** [Applicants' emphasis acknowledged] and that the formation of the two or more different cross-linking bonds is required for increased stability.

In response, the Examiner respectfully disagrees and maintains that Applicants' instant method is considered as being anticipated for the reasons already made of record, namely the teachings of Example 6 as well as claims 1 and 4. The Examiner also respectfully submits that Applicants' remarks continue to be directed to a purported physical property of the composition prepared using the instantly claimed method. Applicants have presented no amendments or arguments concerning the method or materials used by the reference.

Concerning Applicants' remarks which are directed to the linking of HA molecules by means of two different types of bonds, the Examiner respectfully further points out that the method of claim 6 teaches using 1,2,7,8-diepoxyoctane, thereby teaching the limitations of claim 1. The added preferred teachings of crosslinking agents such as butanediol diglycidyl ether, in claim 4, provides a teaching which further and expressly anticipates Applicants' instant invention where it is further limited at claims 40 and 41. Stated another way, Applicants' instant claims are read upon by the prior art where both the method and components are the same. Thus,

"[w]here the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established." (see MPEP §2112.01(I)). Since the teachings of Zhao employ the instantly claimed method, using the instantly claimed components, it follows, absent a clear showing of evidence to the contrary, that the invention of Zhao results in the instantly claimed composition.

Furthermore, the Office does not have the facilities for examining and comparing the compositions prepared using Applicants' instantly claimed method with those which are prepared by Zhao et al., alone or in combination with Malson in order to establish that the prior art does not possess the same material structural and functional characteristics of the claimed composition. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed methods/products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Lastly, in light of the forgoing, Applicants' previously filed Rule 132 Declaration, filed 22 September 2009, has been reviewed and considered again. The Examiner respectfully maintains that there is nothing submitted within said affidavit which appears to compare the instantly claimed method to that which is taught in the art. The Examiner acknowledges Applicants' discussion directed to current market leaders of gels (e.g. Juvederm® and Restylane®). However, as it appears that neither of these trademarked products is discussed by the Zhao reference, it would appear that the scope of the affidavit is not commensurate in scope

with Applicants' arguments.

A clear, side-by-side, comparative (i.e. experiment and data) showing of the differences between Applicants' instant invention and the resulting product against the method and product of the prior art would give the Examiner reason to reconsider the previous rejections.

Concerning Applicants' remarks directed to the combined teachings of Zhao and Malson, Applicants first present the same argument on behalf of Zhao and further state that "[e]ven if the reaction conditions taught by Malson are combined with Zhao, the combined teachings would not lead one of ordinary skill in the art to the presently claimed invention" for the reasons already discussed above, regarding Zhao. Further concerning Malson, Applicants' argue that the language is quite clear that the language of steps (a) and (b) of claim 36 do not involve the removal of excess epoxide from the alkaline medium until after the drying step has concluded.

In response to the first remark, the Examiner respectfully points to the response above, already made of record.

Concerning the latter argument, the Examiner respectfully disagrees with Applicants' position, and further points out that Applicants' instant method recites "comprising" language (MPEP §2111.03). Otherwise stated, a step in the art which teaches the removal of excess epoxide is not necessarily precluded by the invention as instantly claimed.

Furthermore, step (b) of the instant method recites that the cross-linked polysaccharide is dried without "substantially removing" epoxide from the medium to form the cross-linked matrix. The Examiner has reviewed the instant disclosure for further clarification and definition as to how much epoxide can be removed from the instantly claimed cross-linking reaction

system before it is considered to be a "substantial" removal (i.e. how much can be removed without impeding HA cross-linking). No such clarification or definition was found. As such, the Examiner reasonably concludes that the removal of only "excess" epoxide from the Zhao reaction, does read on the instantly recited method of step (b), particularly because the matrix is still formed despite the removal of the excess epoxide. As such the art is interpreted as teaching that a "substantial" amount of epoxide is not removed from the medium (e.g. an amount necessary to facilitate cross-linking) prior to the drying and formation of the matrix.

For these reasons, Applicants' arguments are found unpersuasive. Said rejection is therefore **maintained** and, in light of the discussion above (see **CLAIM OBJECTION**), necessarily extended to include the limitations of the newly added claim 70.

All claims under consideration remain rejected; no claims are allowed.

CONCLUSION

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

CORRESPONDENCE

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey T. Palenik/
Examiner, Art Unit 1615

/Robert A. Wax/
Supervisory Patent Examiner, Art Unit 1615